

## IT IS CLAIMED:

1. A pharmaceutical composition effective in treating an inflammatory condition in mammalian subject, comprising a pharmaceutically effective dosage of an alpha-9 integrin antagonist compound and a pharmaceutical excipient.

2. The pharmaceutical composition of claim 1, wherein said inflammatory condition is characterized by increased neutrophil adhesion.

3. The pharmaceutical composition of claim 1, wherein said alpha-9 antagonist compound inhibits binding between alpha-9 integrin and an alpha-9 integrin ligand.

4. The pharmaceutical composition of claim 3, wherein said alpha-9 integrin antagonist compound exhibits a potency in inhibiting binding between alpha-9 integrin and an alpha-9 integrin ligand that is at least 1/1000 as high an inhibitory potency exhibited by a compound selected from the group consisting of:

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamoyloxy) phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

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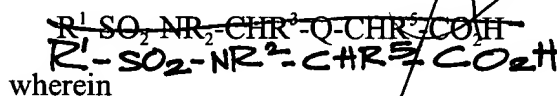
5. The pharmaceutical composition of claim 3, wherein said alpha-9 integrin antagonist compound is effective in inhibiting binding between alpha-9 integrin and an alpha-9 integrin ligand as evidenced by an  $IC_{50}$  for such inhibition of less than about 100  $\mu M$ .

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6. The pharmaceutical composition of claim 5, wherein said alpha-9 integrin antagonist compound is a selected from a group of compounds which inhibit alpha-4/beta-1 integrin binding to an alpha-4/beta-1 integrin ligand.

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7. The pharmaceutical composition of claim 1, wherein said compound is selected from the group consisting of compounds having the formula:



wherein

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$R^1$  is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

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$R^2$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and  $R^1$  and  $R^2$  together with the nitrogen atom bound to  $R^2$  and the  $SO_2$  group bound to  $R^1$  can form a heterocyclic or a substituted heterocyclic group;

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$R^3$  is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when  $R^2$  does not form a

heterocyclic group with  $R^1$ ,  $R^2$  and  $R^3$  together with the nitrogen atom bound to  $R^2$  and the carbon atom bound to  $R^3$  can form a heterocyclic or a substituted heterocyclic group;

$R^5$  is  $-(CH_2)_x-Ar-R^{5'}$  where  $R^{5'}$  is selected from the group consisting of

$-O-Z-NR^8R^{8'}$  and  $-O-Z-R^{12}$  wherein  $R^8$  and  $R^{8'}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where  $R^8$  and  $R^{8'}$  are joined to form a heterocycle or a substituted heterocycle,  $R^{12}$  is selected from the group consisting of heterocycle and substituted heterocycle, and  $Z$  is selected from the group consisting of  $-C(O)-$  and

$-SO_2-$ ,

$Ar$  is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

$x$  is an integer of from 1 to 4;

$Q$  is  $-C(X)NR^7-$  wherein  $R^7$  is selected from the group consisting of hydrogen and alkyl; and  $X$  is selected from the group consisting of oxygen and sulfur; and pharmaceutically acceptable salts thereof.

8. The pharmaceutical composition of claim 1, wherein said alpha-9 integrin antagonist is selected from the group consisting of

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyloxy)  
phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

9. A pharmaceutical composition for treating an inflammatory condition in a  
mammalian subject, comprising

a pharmaceutical excipient; and

a small molecule compound selected for its ability to inhibit binding  
between alpha-9 integrin and an alpha-9 integrin ligand, as evidenced by said  
molecule exhibiting a potency in an alpha-9 integrin-alpha-9 integrin ligand  
binding assay that is at least 1/1000 as high as a potency of a compound  
selected from the group consisting of:

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyloxy)phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

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10. The pharmaceutical composition of claim 9, wherein said compound is an inhibitor of alpha-4/beta-1 integrin binding to VCAM-1, as evidenced by its ability to inhibit said binding with a potency that is at least 1/1000 as high as a potency exhibited by a compound selected from the group consisting of:

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N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

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N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

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N-(toluene-4-sulfonyl)-L-[1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyloxy)phenylalanine, and

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N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

11. A method of screening for therapeutic compounds effective in treating an inflammatory condition, comprising

adding a test compound to an assay system which measures an amount of alpha-9 integrin binding to an alpha-9 integrin ligand, and

selecting the test compound as an effective therapeutic drug candidate, if said compound exhibits a binding inhibitory activity that is at least 1/1000 as potent as an activity exhibited by a compound selected from the group consisting of:

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyloxy)phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

12. The method of claim 11, wherein said inflammatory condition includes increased neutrophil adhesion.

13. The method of claim 11, wherein said test compound is selected from a group of compounds that inhibit binding of alpha-4/beta-1 integrin to an alpha-4/beta-1 integrin ligand.

14. The method of claim 13, wherein said group of alpha-4/beta-1 integrin inhibitory compounds exhibit an inhibitory potency that is at least 1/1000 as high as an inhibitory potency exhibited by a compound selected from the group consisting of:

- 5 N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,  
N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,  
N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,  
10 N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,  
N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,  
15 N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,  
N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine,  
N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyloxy)phenylalanine, and  
20 N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

15. The method of claim 14, wherein said inhibition of binding of alpha-4/beta-1 integrin is measured in a test assay that measures binding of said alpha-4/beta-1 integrin molecule to VCAM-1.

16. The method of claim 13, wherein said test compound is selected from a group of carbamyl compounds having the formula:  $R^1-SO_2-NR_2-CHR^3-Q-CHR^5-CO_2H$   
wherein

$R^1$  is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

$R^2$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and  $R^1$  and  $R^2$  together with the nitrogen atom bound to  $R^2$  and the  $SO_2$  group bound to  $R^1$  can form a heterocyclic or a substituted heterocyclic group;

$R^3$  is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when  $R^2$  does not form a heterocyclic group with  $R^1$ ,  $R^2$  and  $R^3$  together with the nitrogen atom bound to  $R^2$  and the carbon atom bound to  $R^3$  can form a heterocyclic or a substituted heterocyclic group;

$R^5$  is  $-(CH_2)_x-Ar-R^{5'}$  where  $R^{5'}$  is selected from the group consisting of  $-O-Z-NR^8R^{8'}$  and  $-O-Z-R^{12}$  wherein  $R^8$  and  $R^{8'}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where  $R^8$  and  $R^{8'}$  are joined to form a heterocycle or a substituted heterocycle,  $R^{12}$  is selected from the group consisting of heterocycle and substituted heterocycle, and  $Z$  is selected from the group consisting of  $-C(O)-$  and

$-SO_2-$ ,

$Ar$  is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

$x$  is an integer of from 1 to 4;

$Q$  is  $-C(X)NR^7-$  wherein  $R^7$  is selected from the group consisting of hydrogen and alkyl; and  $X$  is selected from the group consisting of oxygen and sulfur; and pharmaceutically acceptable salts thereof.



17. The method of claim 11, wherein said alpha-9 integrin antagonist is selected from the group consisting of

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyloxy)phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

18. A method of treating an inflammatory condition in mammalian subject, comprising administering to the subject a pharmaceutically effective dosage of an alpha-9 integrin antagonist compound.

19. The method of claim 18, wherein said inflammatory condition is characterized by increased neutrophil adhesion.

20. The method of claim 18, wherein said alpha-9 integrin antagonist compound is a selected from a group of compounds which inhibit alpha-4/beta-1 integrin binding to an alpha-4/beta-1 integrin ligand.

21. The method of claim 18, wherein said alpha-9 integrin antagonist compound exhibits a potency in inhibiting binding between alpha-9 integrin and an alpha-9 integrin ligand that is at least 1/1000 as high as an inhibitory potency exhibited by a compound selected from the group consisting of:

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo)thiamorpholin-3-carbonyl]-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and  
N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyloxy)phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

22. The method of claim 18, wherein said compound is selected from the group consisting of carbamyl compounds having the formula:  $R^1-SO_2-NR_2-CHR^3-Q-CHR^5-CO_2H$

wherein

$R^1$  is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

$R^2$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and  $R^1$  and  $R^2$  together with the nitrogen atom bound to  $R^2$  and the  $SO_2$  group bound to  $R^1$  can form a heterocyclic or a substituted heterocyclic group;

$R^3$  is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when  $R^2$  does not form a heterocyclic group with  $R^1$ ,  $R^2$  and  $R^3$  together with the nitrogen atom bound to  $R^2$  and the carbon atom bound to  $R^3$  can form a heterocyclic or a substituted heterocyclic group;

$R^5$  is  $-(CH_2)_x-Ar-R^{5'}$  where  $R^{5'}$  is selected from the group consisting of  $-O-Z-NR^8R^{8'}$  and  $-O-Z-R^{12}$  wherein  $R^8$  and  $R^{8'}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where  $R^8$  and  $R^{8'}$  are joined to form a heterocycle or a substituted heterocycle,  $R^{12}$  is selected from the group consisting of heterocycle and substituted heterocycle, and  $Z$  is selected from the group consisting of  $-C(O)-$  and

$-SO_2-$ ,

$Ar$  is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

$x$  is an integer of from 1 to 4;

$Q$  is  $-C(X)NR^7-$  wherein  $R^7$  is selected from the group consisting of hydrogen and alkyl; and  $X$  is selected from the group consisting of oxygen and sulfur; and pharmaceutically acceptable salts thereof.

23. The method of claim 18, wherein said alpha-9 integrin antagonist is selected from the group consisting of:

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

5 N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

10 N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl]-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and  
N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamoyloxy)  
phenylalanine, and

15 N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

add C1  
add E6

add C1  
add E6